Remarks

This amendment is of an entirely editorial nature. The misspelling of the word "Neuro-chem" has been corrected, and at two locations the abbreviation et al. has been reformatted to *et al.*

Version of amended paragraph on page 7 spanning from line 13 to line 27 with underline markings to show changes made

Likewise, numerous publications have reported genetic forms of Alzheimer's disease [Campion *et al.*[et al.] Neurology 45(1):80-85 (1995)]. A Medline database search from 1976 to April 1995 for references addressing familial Alzheimer's disease and stress proteins generated only one match [Guillemette *et al.*[et al.], J. Neurochem. [J. Neuro-chem.] 47(3):987-997 (1986], but actually this paper did not mention that any of its Alzheimer patients had a genetic form of the disease. The report by Guillemette *et al.* described studies on RNA transcripts obtained from post-mortem Alzheimer's brain biopsy samples. They observed elevated levels of hsp mRNA transcripts in brain samples from Alzheimer patients who had fever immediately prior to death. They also studied human brain mRNA translation (i.e., protein) products. Guillemette *et al.* reported, in part, that

Clean version of paragraph on page 19 spanning from line 7 to line 17

Each experiment contains the following six sections: (a) patient cells grown under standard culture conditions; (b) control cells grown under standard culture conditions; (c) patient cells grown under standard culture conditions in the presence of a candidate therapeutic drug; (d) control cells grown under standard culture conditions in the presence of a candidate therapeutic drug; (e) control cells grown in presence of a stress protein inducing parameter (i.e., sodium arsenite or ethanol [Pratt and coworkers, 1989]); and (f) control cells grown in the presence of a stress protein inducing factor and a candidate therapeutic drug.

Remarks

This amendment is of an entirely editorial nature. In the application as filed,

Page 19 section (a) corresponds to claim 1 part c(1)
Page 19 section (b) corresponds to claim 1 part c(3)
Page 19 section (c) corresponds to claim 1 part c(2)
Page 19 section (d) corresponds to claim 1 part c(4)
Page 19 section (e) corresponds to claim 1 part c(5)
Page 19 section (f) corresponds to claim 1 part c(6)

The present amendment serves to more clearly delineate these sections. This section of the Specification and Claim 1, part c describe the same six experimental circumstances. But the order in which they are listed is slightly different. Page 19 section (b) corresponds to claim 1 part c(3) and Page 19 section (c) corresponds to claim 1 part c(2). This amendment serves to modify the order of listing in the Specification, to that it will be exactly the same order as listed in Claim 1, part c. This changes nothing in terms of how the invention is used, but this slight difference in ordering between the Specification and the Claims in the application as filed might serve to confuse the reader. Any such editorial error should be removed by amendment.

Version of amended paragraph on page 19 spanning from line 7 to line 17 with underline markings to show change made

Each experiment contains the following six sections: (a) patient cells grown under standard culture conditions; (b) control cells grown under standard culture conditions; (c) [(b)] patient cells grown under standard culture conditions in the presence of a candidate therapeutic drug; [(c) control cells grown under standard culture conditions;] (d) control cells grown under standard culture conditions in the presence of a candidate therapeutic drug; (e) control cells grown in presence of a stress protein inducing parameter (i.e., sodium arsenite or ethanol [Pratt and coworkers, 1989]); and (f) control cells grown in the presence of a stress protein inducing factor and a candidate therapeutic drug.

Clean version of paragraph on page 19 spanning from line 18 to line 24

When tested within such an experimental protocol, candidate therapeutic agents which address the specific disease etiology will not prevent chemically induced stress protein expression [section (f)], but will prevent stress protein expression in the genetic disease cell strains [section (b)]. Sections (a, (c), (d), and (e) represent various comparative controls which further characterize the drug screening system.

Remarks

This amendment is of an entirely editorial nature. The term "[section(f)]" is appropriately added to more explicitly identify section (f).

Version of amended paragraph on page 19 spanning from line 18 to line 24 with underline marking to show change made

When tested within such an experimental protocol, candidate therapeutic agents which address the specific disease etiology will not prevent chemically induced stress protein expression [section (f)], but will prevent stress protein expression in the genetic disease cell strains [section (b)]. Sections (a, (c), (d), and (e) represent various comparative controls which further characterize the drug screening system.

Clean version of paragraph on page 19 spanning from line 18 to line 24

When tested within such an experimental protocol, candidate therapeutic agents which address the specific disease etiology will not prevent chemically induced stress protein expression, but will prevent stress protein expression in the genetic disease cell strains [section (b)]. Sections (a), (c), (d), and (e) represent various comparative controls which further characterize the drug screening system.

Remarks

This amendment is of an entirely editorial nature. The misspelling of the term "(a" has been corrected.

Version of amended paragraph on page 19 spanning from line 18 to line 24 with markings to show change made

When tested within such an experimental protocol, candidate therapeutic agents which address the specific disease etiology will not prevent chemically induced stress protein expression, but will prevent stress protein expression in the genetic disease cell strains [section (b)]. Sections (a) [(a)], (c), (d), and (e) represent various comparative controls which further characterize the drug screening system.

Clean version of paragraph on page 19 spanning from line 18 to line 24

When tested within such an experimental protocol, candidate therapeutic agents which address the specific disease etiology will not prevent chemically induced stress protein expression, but will prevent stress protein expression in the genetic disease cell strains [section (c)]. Sections (a, (c), (d), and (e) represent various comparative controls which further characterize the drug screening system.

Remarks

This amendment is of an entirely editorial nature. After amending the paragraph immediately above in the Specification so as to define original section (c) as amended section (b) and original section (b) as amended section (c), it is now necessary to correspondingly amend this paragraph so that mention of original section (b) is replaced by amended section (c).

Version of amended paragraph on page 19 spanning from line 18 to line 24 with markings to show change made

When tested within such an experimental protocol, candidate therapeutic agents which address the specific disease etiology will not prevent chemically induced stress protein expression, but will prevent stress protein expression in the genetic disease cell strains [section (c)] [[section (b)]]. Sections (a, (c), (d), and (e) represent various comparative controls which further characterize the drug screening system.

Clean version of paragraph on page 21 spanning from line 2 to line 11

Such assay variations may have useful applications as alternative procedures for screening of candidate therapeutic drugs. The method of this invention may be applied for use with fibroblasts obtained from patients having a genetic neurodegenerative disease selected from the group consisted of Charcot-Marie-Tooth disease, familial Alzheimer's disease, familial Parkinson's disease, Huntington's disease, spinal muscular atrophy, Friedreich's ataxia, giant axon neuropathy, juvenile ceroid-lipofuscinosis, familial motor neuron diseases, juvenile diabetic polyneuropathy and Down's syndrome, including various individual genetic subvarieties thereof.

Remarks

This amendment is of an entirely editorial nature. The misspelling of the word "Friedreich'a" has been corrected.

Version of amended paragraph on page 21 spanning from line 2 to line 11 with markings to show change made

Such assay variations may have useful applications as alternative procedures for screening of candidate therapeutic drugs. The method of this invention may be applied for use with fibroblasts obtained from patients having a genetic neurodegenerative disease selected from the group consisted of Charcot-Marie-Tooth disease, familial Alzheimer's disease, familial Parkinson's disease, Huntington's disease, spinal muscular atrophy, Friedreich's [Friedreich'a] ataxia, giant axon neuropathy, juvenile ceroid-lipofuscinosis, familial motor neuron diseases, juvenile diabetic polyneuropathy and Down's syndrome, including various individual genetic subvarieties thereof.

Clean version of paragraph on page 24 spanning from line 19 to line 20

2. Methodology Useful in the Characterization of Diagnostic Procedures

Remarks

This amendment is of an entirely editorial nature, and serves to better delineate the use of the instant disclosure as a drug screening method from the use of the instant disclosure as a diagnostic procedure. On page 24 the following section title in the Specification

Methodology Useful in the Characterization
of Diagnostic Procedure .

is presently amended with the left margin justified section title "2. Methodology Useful in the Characterization of Diagnostic Procedures"

Version of amended section title on page 24 spanning from line 19 to line 20 with markings to show change made

[Methodology Useful in the Characterization of Diagnostic Procedure]

2. Methodology Useful in the Characterization of Diagnostic Procedures

Remarks

This amendment is of an entirely editorial nature. As per examiner's Point (4), in Claim 1, part c the spelling of the word "concomitent" has been corrected.

Version of amended Claim 1 with markings to show change made

1. A method for selecting a drug candidate agent or composition of more than one drug candidate agent of possible clinical value in the treatment of a neurological disease comprising

b. establishing, from a patient having a predetermined neurological disease, a cell culture of fibroblast cells;

b. establishing, from a person not having the predetermined neurological disease, a control cell culture of fibroblast cells;

c subsequent <u>concomitant</u> [concomitant] cell culture growth of (1) a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease; (2) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease; (3) a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease grown in the presence of an agent being investigated; (4) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of an agent being investigated; (5) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of a chemical stress protein-inducing parameter; and (6) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of the stress protein-inducing parameter and the agent being investigated; and

d. use of an indicator system capable of detecting stress protein expression in said culture fibroblast cells to identify as a drug candidate of possible clinical value that agent which does not prevent chemically induced stress protein expression in the control cell culture as per step c(6) but which does prevent stress protein expression in the patient cell culture as per step c(3).

Remarks

This amendment is in response to the examiner's Point (6) on page 4 of the Office letter stating that "...the claims as written include all neurological diseases." The first complete paragraph on page 21 of the Specification includes a closed group of diseases to which this disclosure relates. The present amendment incorporates this list of diseases into Claim 1.

Version of amended Claim 1 with markings to show change made

1. A method for selecting a drug candidate agent or composition of more than one drug candidate agent of possible clinical value in the treatment of a neurological disease selected from the group consisting of Charcot-Marie-Tooth disease, familial Alzheimer's disease, familial Parkinson's disease, Huntington's disease, spinal muscular atrophy, Friedreich's ataxia, giant axon neuropathy, juvenile ceroid-lipofuscinosis, familial motor neuron diseases, juvenile diabetic polyneuropathy and Down's syndrome comprising

d. establishing, from a patient having a predetermined neurological disease, a cell culture of fibroblast cells;

b. establishing, from a person not having the predetermined neurological disease, a control cell culture of fibroblast cells;

c subsequent concomitent cell culture growth of (1) a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease; (2) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease; (3) a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease grown in the presence of an agent being investigated; (4) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of an agent being investigated; (5) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of a chemical stress protein-inducing parameter; and (6) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of the stress protein-inducing parameter and the agent being investigated; and

d. use of an indicator system capable of detecting stress protein expression in said culture fibroblast cells to identify as a drug candidate of possible clinical value that agent which does not prevent chemically induced stress protein expression in the control cell culture as per step c(6) but which does prevent stress protein expression in the patient cell culture as per step c(3).

Remarks

As an editorial change intended to further distinguish between the aspect of the instant disclosure relating to its use as a drug screening method and the aspect of its use as a diagnostic procedure, the applicant is presently amending the text section title on page 24 entitled "Methodology Useful in the Characterization of Diagnostic Procedures" as noted above. The amended text section title is "2."Methodology Useful in the Characterization of Diagnostic Procedures." So, for the reader this more distinctly delineates the text section starting on Specification page 24 from the text section entitled "1.Drug Screening Methodology" starting on Specification page 11.

Point (2) of the Examiner's letter

The Examiner stated in part that "The tryptan [sic] blue assay measures whether or not cells are dead or alive, and since excessive stress protein expression is correlated with cell death the assay used by May is an indicator system capable of detecting stress protein expression." The Applicant once again disagrees with the Examiner's assertion that "...the [trypan blue] assay used by May is an indicator system capable of detecting stress protein expression." This statement by the Examiner indicates a basic misunderstanding of the science to which he refers. This conclusion by the Applicant can be documented as follows. A PubMed literature search by the Applicant on 29 January 2006 on the quoted term "trypan blue" generated **5,743** citations (see attached copy of first page). A PubMed literature search by the Applicant on 29 January 2006 on the quoted term "stress protein" generated **1,291** citations (see attached copy of first page). A PubMed literature search by the Applicant on 29 January 2006 on the combined quoted terms "trypan blue" AND "stress protein" generated **two** citations (see attached copy). These biomedical literature search results fail to support the Examiner's attempt to equate the trypan blue assay with stress protein induction.

But the combined quoted terms "trypan blue" AND "stress protein" did generate two citations. Do these two citations support the Examiner's attempt to equate the trypan blue assay with stress protein induction? The answer is that they clearly do not. One of these citations is SD Morris *et al.* (*J. Clin. Invest.* 97:706-12, 1996, copy attached hereto). On page 707 they stated that "...blots were probed with mAbs specific for the inducible isoform of hsp70 (hsp72) (C92F3A-5; Stressgen, Victoria B.C., Canada) or with mAbs specific for both constitutive and inducible isoforms (hsp73 and -72, respectively)..." Hence, they used Western blotting to measure stress protein induction, not the trypan blue assay. On page 708 they stated "*Trypan blue exclusion.* After lethal heat stress or simulated ischemia, the cells were washed with PBS, trypsinized for 2 min in 0.25 mg/ml trypsin in versine (GIBCO BRL), and then neutralized with neonatal calf serum. Cells were then centrifuged, the supernatant was aspirated, and the cardiocytes were resuspended in 300 ml of PBS. A 20-ml aliquot of cell suspension was then added to an equal volume of trypan blue, and the percentage of dead (blue) cells was determined using a hemocytometer. To establish that the administration of these drugs did not have a directly toxic effect upon the cardiocytes, trypan blue exclusion was also performed at 4 and 24 h after incubation with herbimycin-A or genistein, in comparison with controls, without lethal stress." This statement clearly indicates that the trypan blue assay was merely being used to measure "dead (blue) cells." Unlike the Examiner, Morris *et al.* do not equate the trypan blue assay with measurement of stress proteins. If, like the Examiner, Morris *et al.* equated the trypan

blue assay with the measurement of stress proteins, than why would they have bothered to use two different assay systems (i.e., Western blotting and the trypan blue assay)? The answer is that Morris *et al.* recognized that these two different assay systems measure two fundamentally different things, while the examiner does not.

The other citation is SC Borkan *et al.* [*Am. J. Physiol.* 265(3Pt2):F333-41, 1993, copy attached hereto]. On pages F333-F334, Borkan *et al.* state "To elicit heat stress response characterized by accumulation of HSP 72...The samples were subjected to 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE; Bio-Rad, Richmond, CA) followed by immunoblot analysis as previously described by our laboratory (12)." Hence, here too Western blotting was used to measure stress protein presence. On page F334, Borkan *et al.* state "*Trypan blue uptake.* To assess cell membrane permeability, 12-well trays of confluent IMCD cells were incubated at the desired temperature for 1 h. The medium from each well was removed and replaced with 0.5 ml of sterile filtered 1% trypan blue and incubated at 25°C for l0-15 min. Each well was examined with an inverted microscope fitted with a counting grid inserted into the eyepiece. Five random fields of 100 cells each were examined for trypan blue staining by an observer blinded to the protocol conditions, and the mean number of dye-stained cells was calculated." Hence, here Borkan *et al.* used the trypan blue assay to measure "cell membrane permeability" as an indicator of cell death. Someone of ordinary skill in the art knows that the trypan blue assay measures whether cells are alive or not by measuring their ability to actively *exclude* the dye from entering each cell. Only living cells can do this. Dead cells have high membrane permeability, and therefore trypan blue readily enters them. But this is not an indicator of stress protein presence. Like Morris *et al.*, Borkan *et al.* used two different assay systems to measure either the presence of stress protein or to measure cell death.

Hence, looking at the 5,743 PubMed literature citations for the term "trypan blue," the Examiner's assertion that "...the assay used by May is an indicator system capable of detecting stress protein expression" is completely without support. The Applicant states once again that May and Gray (1985) never mentioned anything pertaining to stress proteins or stress protein presence. That the Examiner insists on *his personal interpretation* that May and Gray (1985) really were describing research on stress protein induction, even though the investigators never stated or suggested this, is nothing more than a view held exclusively by the Examiner.

On these grounds, the Applicant remains in opposition to the Examiner's final election/ restriction requirement. The grounds for the Examiner's decision are nothing more than a personal misunderstanding on his part and are completely unsupported by a review of the prior art.

Point (3) of the Examiner's letter

The Examiner has noted that since the Applicant included prior art references within the text of the Specification and not on a separate sheet of paper, that the Examiner refused to consider the Applicant's discussion of said prior art. The Applicant notes that this communication includes an amendment that is a list of the cited prior art intended to be inserted at the end of the Specification. The Applicant also notes his understanding that the Examiner's reference to this *pro forma* editorial objection as a basis for not considering the Applicant's prior art discussion whatsoever is an action on the part of the Examiner that is entirely disproportionate to the cited editorial error. Such an action

on the part of the Examiner brings into question the Examiner's willingness to consider the disclosure on its merits.

Point (4) of the Examiner's letter

As noted above, the Applicant is hereby amending Claim 1 so as to replace the misspelled word "concomitent" with the word "concomitant."

Points (5) and (6) of the Examiner's letter

In these points, the Examiner has cited 35 U.S.C. § 112 as a basis for claims rejection. In point (6) the Examiner noted that "...because the specification, while being enabling for a method of contacting cultured fibroblasts with agents under investigation wherein the pathological mechanism is manifest in both neural cells and fibroblasts, does not reasonably provide enablement for a method of screening for drugs which are candidates for treatment of all neurological diseases, or for determining whether or not the agent in the screening assay should be selected as a drug candidate agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims" The Examiner then went on to list eight factors that characterize enablement. Such *pro forma* policy statements on the part of the Examiner stand in contrast to the detailed enabling disclosure contained within the Specification.

In the above quoted statement, the Examiner asserts that the applicant has claimed that the instant disclosure has utility as a research tool useful for identifying candidate drugs "...for treatment of all neurological diseases" (Office action page 3). This assertion by the Examiner is false. In fact, it is an assertion only by the Examiner, not the Applicant.

The Examiner stated that "However, the claims as written include ***all*** [emphasis added] neurological diseases" (Office action, page 4). In fact, the claims as written are dependent upon and limited by the Specification. On page 4 of the Office action, the Examiner asserted that the claims as written could relate to "schizophrenia, febrile seizures, Korsakoff's syndrome, spongiform encephalopathies..." The Applicant presently notes that such neurological disorders were never mentioned in the Specification and do not lie within the metes and bounds of the instant disclosure.

On Specification page 21, lines 4 – 12, the Applicant mentioned that "The method of this invention may be applied for use with fibroblasts obtained from patients having a genetic neurodegenerative disease selected from the group consisting of Charcot-Marie-Tooth disease, familial Alzheimer's disease, familial Parkinson's disease, Huntington's disease, spinal muscular atrophy, Friedreich'a [sic] ataxia, giant axon neuropathy, juvenile ceroid-lipofuscinosis, familial motor neuron diseases, juvenile diabetic polyneuropathy and Down's syndrome, including various individual genetic subvarieties thereof." This language explicitly defines the metes and bounds of the group of human diseases addressed in the instant disclosure. This language includes use of the phrase "selected from the group consisting of," which is ***limiting*** language. This language does not include use of the phrase "such as," which is indefinite and not limiting. This language in no way refers to "schizophrenia, febrile seizures, Korsakoff's syndrome, spongiform encephalopathies...," which are inferences envisioned solely by the Examiner that ***do not*** fall within the scope of the invention as disclosed by the Applicant. On these grounds, the Examiner's assertion on Office action page 3 that

"...the specification...does not reasonably provide enablement for a method of screening for drugs which are candidates for treatment of ***all*** [emphasis added] neurological diseases" is without merit and incorrect.

Also, on page 4 of the Office action the Examiner stated that "The claims are broad in that they are drawn to assays to find drugs for treatment of ***any*** [emphasis added] disease." Here too, the Examiner's conclusion is incorrect. Once again, the Examiner's attention is drawn to the Applicant's limiting statement as quoted in the preceding paragraph.

On another issue raised in section (6) of the Office action, on page 3 the Examiner stated that "...the specification...does not reasonably provide enablement for a method of screening for drugs which are candidates for treatment of all neurological diseases, or for determining whether or not the agent in the screening assay should be selected as a drug candidate agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." Likewise, in the last paragraph of page 4 of the Office action, the Examiner asserted that "...a skilled artisan would have to resort to undue experimentation in order to practice these methods..."

Here too, the Applicant notes that such an objection was both anticipated by and correctly addressed in the disclosure as filed. Pages 11 – 24 of the Specification include a section entitled "Drug screening methodology." In the first part of this section on pages 11 – 18 the establishment of the method is illustrated by example using fibroblasts obtained from normal human donors and patients having a form of Charcot-Marie-Tooth disease, a syndrome of clinically similar genetic peripheral neuropathies. The first paragraph of this section includes the statement that "...the present invention is based on the monitoring of one or more qualitative metabolic markers, i.e., the appearance of stress proteins and possibly other proteins secondarily related to disease etiology in cultured fibroblasts." The Applicant's text then goes on to explain the laboratory methodology in great detail. For example, the penultimate three lines on page 12 explicitly define the tissue culture media in which fibroblasts were grown and lines 4 – 20 on page 13 explicitly define the experimental conditions for gel electrophoresis. The Applicant's disclosure then goes on for another five pages, providing further methodological details regarding the Applicant's previous work on Charcot-Marie-Tooth and control donor fibroblasts. This level of detailed disclosure is in fact enabling for one of ordinary skill in the art and does not require undue experimentation. Contrary to the examiner's view, the methodology is stated directly. The two-dimensional gel electrophoresis data example pertaining to skin fibroblasts derived from patients having a form of Charcot-Marie-Tooth disease is in fact the practical basis of a working example of the method of the invention. In order to use the example described, one of ordinary skill in the art need merely add an experimental drug or drugs and observe the subsequent effects as defined explicitly in the disclosure.

Then in the Specification section spanning from page 18, line 18 to page 20, line 7 the applicant has gone on to explicitly describe how one of ordinary skill in the art can use this invention as a drug screening method. The section spanning from page 20, line 8 to page 24, line 18 discloses various permutations of the basic drug screening assay method. Here again, in these sections on pages 18 – 24 detailed teaching of the method is provided. One of ordinary skill in the art knows that he/she is not required to practice every conceivable permutation of the disclosure. The investigator of ordinary

skill in the art need only select those particular details with which he/she is already familiar with or interested in putting to use, and then use those particular aspects of the disclosure.

The Examiner stated that the Specification is not enabling, that the Specification provides a lack of guidance and that the Specification requires undue experimentation. As a particular and explicit response to these related statements, the Applicant wishes to draw the Examiner's attention to the Specification section on page 19, lines 7 – 24 spanning from "Each experiment contains the following six sections..." to "...characterize the drug screening system." This text section briefly summarizes the new and novel drug screening assay.

Also in point (6) of the Office action on page 5 the Examiner noted that "...the specification does not in fact provide working examples of the screening assay. There is no disclosure of experiments in which the method as claimed was performed." The Applicant presently notes that in this statement the Examiner is misrepresenting the relevant USPTO requirement. The Applicant acknowledges that it would be desirable to have provided still more information than the disclosure contains, in effect "taking the person of ordinary skill in the art by the hand" and descriptively walking him/her through a demonstrated record of the use of the candidate drug screening method to identify a new substance of potential clinical therapeutic value. But this is not the relevant USPTO requirement.

The relevant USPTO requirement is simply to provide enabling detail, so that one of ordinary skill in the art can practice the invention if he/she wishes to do so. This includes the concept of "prophetic invention." Prophetic inventions are allowable according to USPTO policy, as long as the prophetic invention (1) provides an enabling degree of detail in its disclosure and (2) is based on a reasonable interpretation of available scientific information. The instant disclosure does in fact provide enabling detail, so one of ordinary skill in the art can practice it. Such enabling detail serves to distinguish between an invention that can be practiced as described in the disclosure from something which is merely a theory. The instant disclosure also includes extensive reference to related scientific methods and information, and is reasonable within this context. However, the Applicant has no obligation to provide routine methodological details that are available from public information sources and are well known to those of ordinary skill in the art.

The Applicant also wishes to note, by way of precedent, that two of his previously issued US patents include examples of prophetic methods for treatment of human diseases. The first of these is US Patent number 6,444,221 (see Claims 1-8, 18 and 19), and the second is US Patent number 6,746,678 (see Claims 1-33). In these two US patents, almost all of the approved claims were issued *on a prophetic basis.* Hence, the Examiner's present objection that "...the specification does not in fact provide working examples of the screening assay. There is no disclosure of experiments in which the method as claimed was performed" is unreasonable, contrary to USPTO precedent and should be withdrawn.

Also in point (6) of the Office action on page 5 the Examiner noted that "...as claim 1 is presently written it requires the use of an indicator system, but the claim does not guide the artisan sufficiently in how to use that indicator system..." Several indicator systems are described in the Specification. These include the use of silver staining of proteins

as described on page 13, lines 14-20; the use of ELISA methodology as described in the text spanning from pages 19, line 33 to page 20, line 7; and a further detailed summary of indicator systems as described in the text spanning from page 22, line 13 to page 23, line 6. These descriptions of various indicator systems serve to define, in part, the metes and bounds of the invention and serve to *teach* the use of the invention. These descriptions of various indicator systems serve to disclose the full range of utility of the invention to the reader. Knowing that such various indicator systems can be used in the practice of this invention, as the Applicant does, the Applicant would have been remiss to have failed to disclose these indicator systems. Furthermore, the Applicant knows that a patent right is a legal right to *exclude* the practice of an invention by unauthorized parties. Hence, the Applicant would have been remiss in protecting his own legal rights if he had claimed the practice of the invention with use of only one indicator system, but left the use of the **cited** alternative practical indicator systems unclaimed. The Applicant never disclosed the indicator system of May and Gray (1985) because that indicator system would be useless in the attempted practice of the instant disclosure.

As regards the Examiner's statement that ...as claim 1 is presently written it requires the use of an indicator system, but the claim does not guide the artisan sufficiently in how to use that indicator system...," the Applicant also wishes to note that in drafting the instant disclosure, the Applicant had no obligation to disclose information that was already commonly known to those of ordinary skill in the art. Put another way, the invention disclosure need not be a review article. Those of ordinary skill in the art can read the instant disclosure and *decide for themselves* which indicator system cited in the disclosure best fits their individual needs. Different practitioners of the art will have different individual priorities as to which indicator system they may wish to use, and the Applicant has no obligation to make their individual decisions for them.

Also in point (6) of the Office action on page 5 the Examiner noted that "...nor does it [i.e., Claim 1] guide the artisan in deciding which agents under investigation should be selected as drug candidate agents." There is no need for Claims to recapitulate every detail of the invention that was already disclosed in the Specification. In response to this particular objection by the Examiner, the Applicant wishes to draw the Examiner's attention to the Specification section on page 19, lines 7 – 24 spanning from "Each experiment contains the following six sections..." to "...characterize the drug screening system." This text section briefly summarizes the new and novel drug screening assay and explicitly defines the criteria for selecting drug candidate agents worthy of further consideration.

Points (7) and (8) of the Examiner's letter

In point (7) of the Office action, the Examiner stated that the Applicant has failed "...to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In point (8) the Examiner asserted that Claim (1), part (d) failed to define "...what method/process applicant is intending to encompass..." as an indicator system. In fact, the indicator systems are described in the Specification. These include the use of silver staining of proteins as described on page 13, lines 14-20; the use of ELISA methodology as described in the text spanning from pages 19, line 33 to page 20, line 7; and a further detailed summary of indicator systems as described in the text spanning from page 22, line 13 to page 23, line 6. Once particular details of the invention have

been disclosed and defined in the Specification, the Applicant need not recapitulate said details again in the Claims.

Point (9) of the Examiner's letter

Here again, as for Examiner's points (7) and (8), the Examiner has asserted that since information disclosed in the Specification was not recapitulated verbatim in Claims 1-8, that Claims 1-8 fail to set forth "any steps in the process." This is a complete misreading of the stated Claims by the Examiner as well as a denial of the invention disclosure as delineated in the Specification.

Point (10) of the Examiner's letter

The Examiner's statement here is incoherent. The Examiner stated that "The omitted steps are: determining whether or not the agent is a candidate of possible clinical value. Because claim 1, part (d) is indefinite for the reasons enumerated above, the method recited is incomplete." **In fact, the applicant has explicitly defined the criteria for defining whether a substance or combination of substances is a candidate of possible clinical value both in the Specification on page 19, lines 7-24 and in Claim 1, part (d).** How many times does the Applicant have to disclose this? The Applicant is not accountable for the Examiner's inability to grasp the meaning of a concept that has been directly stated. Again, the Examiner's statement that "Merely growing the six cultures concomitantly will not provide the skilled artisan with guidance as to whether or not the agent being investigated qualifies as a drug candidate agent" indicates that the Examiner has completely failed to understand the subject material.

Points (11) and (12) of the Examiner's letter

The Applicant has already discussed the prior art of May and Gray (1985) in Applicant's letter postmarked 20 August 2005. In no way does May and Gray (1985) previously disclose or anticipate the instant disclosure. As previously discussed in detail by the Applicant, the Examiner's citation of May and Gray (1985) represents nothing more than a misrepresentation of the scientific facts. In addition to the Applicant's comments regarding May and Gray (1985) in Applicant's letter postmarked 20 August 2005, the Applicant has further discussed this prior art above in the Remarks section entitled "Point (2) of the Examiner's letter."

In paragraph two of Point (12), the Examiner has attempted to specifically explain how he believes that May and Gray (1985) anticipated the instant disclosure. The Examiner stated that "Furthermore they tested the control culture in the presence of a chemical stress protein-inducing parameter with and without the agent. The chemical stress protein-inducing parameter was 15mM L-HCA (see p. 108, first complete paragraph)." The Applicant has seen page 108, first complete paragraph. They never identified L-HCA or anything else as a "chemical stress protein-inducing parameter." In fact, May and Gray (1985) never identified anything in their article as a "chemical stress protein-inducing parameter." The Examiner's concocted interpretation of May and Gray (1985) is an act never intended by the authors. This is an attempt by the Examiner to read the instant disclosure into the prior art in hindsight.

In order to support his assertion that May and Gray (1985) anticipated the instant disclosure, the Examiner has presented an argument that is flawed in four respects. In

one flawed interpretation, the Examiner has repeatedly inserted wording such as "stress protein expression" or "stress proteins" into his description of the prior art, even though no such wording is really there. The Examiner simply pretends that such wording is there.

In a second flawed interpretation of the cited prior art, the Examiner explicitly and incorrectly asserted that the trypan blue assay is an assay for stress protein expression. In Point (12) the Examiner incorrectly stated once again that "Finally, May et al. used an indicator system capable of detecting stress protein expression. The indictor system was the percentage of cells which are viable; since cells die upon sufficient levels of stress protein the viability assay corresponds to claim 1(d) as viability tests fairly anticipate use of an indicator system." This misinterpretation of the prior art was addressed by the Applicant above in the Remarks section entitled "Point (2) of the Examiner's letter." May and Gray (1985) never expressed the opinion maintained by the Examiner and, as discussed above, a review of the biomedical literature indicates that no one else shares the Examiner's opinion either.

In a third flawed interpretation of the cited prior art, the Examiner continued to ignore what is plainly stated in Claim 1, part d. The Applicant states again, as he has enumerated in his claims as filed, that the claims relate to and depend upon the detection of "stress protein expression" and use thereof to identify drug candidate agents that preferentially suppress stress protein expression in fibroblasts derived from a patient having a pre-determined neurological disease ***not grown in the presence of an added stress protein inducing substance***, while not suppressing stress protein expression in fibroblasts derived from a control fibroblast donor. Some chemical substances might generally suppress stress protein expression, now described by the Applicant as "false hits." These chemical substances are regarded by the Applicant as being of no practical value as drug candidate agents of possible use in clinical treatment of the neurological disease. So, Claim 1 is formatted so as to provide data that makes a clear distinction between chemical substances that are "false hits" and drug candidate agents that preferentially suppress stress protein expression in fibroblasts derived from a patient having a predetermined neurological disease.

In the Examiner's comments of his Point (12), the Examiner has chosen to ignore the statement in the last two sentences of May and Gray (1985) page 108, first complete paragraph. These sentences read "***Similar effects on cell viability were observed in a control culture (730) co-treated with antioxidants and 15 mM L-HCA*** [emphasis added]. In the absence of antioxidants, cell viability was reduced to 30% by L-HCA, but all antioxidants tested improved cell viability to untreated levels (>95%)." In these sentences, May and Gray (1985) directly define what the Applicant ***excluded*** as a false hits according to the definition of "a drug candidate of possible clinical value" in Claim 1, part d.

In paragraph two of Examiner's Point (12), the Examiner attempted to explicitly equate the individual steps of Claim 1 with specific data of May and Gray (1985). As much as any other comments offered by the Examiner, this is where the Examiner attempted to directly explain where in content of Claim 1 was previously disclosed. This is the Examiner's most essential argument cited as grounds for denial of claims allowance. The Examiner mentioned the individual parts of Claim 1 and stated where they were mentioned on either page 103 or page 108 of May and Gray (1985). Yet the Examiner's

statements selectively ignore and misrepresent the essential distinctions between the instant disclosure and said prior art.

In Claim 1, part c(3) the Applicant states "a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease grown in the presence of an agent being investigated." This experimental condition does not include the presence of "a stress protein-inducing parameter" as defined by the Applicant on Specification page 19, lines 14-15. In paragraph two of Examiner's Point (12), the Examiner stated "They [i.e., May and Gray (1985)] also teach culture of the [HD] cells in the presence of a drug candidate agent, namely the antioxidant propyl gallate (see p. 108, first complete paragraph)." Yet the Examiner appears to have not noticed that five lines further down in the same paragraph, May and Gray state that "In the absence of Glu or L-HCA, none of the antioxidants had any effect on [HD] cell number or viability." Hence, May and Gray (1985) teach that when HD fibroblasts are grown in the presence of a candidate drug (i.e., antioxidant) but not in the presence of "a chemical stress protein-inducing parameter" [i.e., the Examiner's assumption that Glu and L-HCA induce stress protein expression] that **no** effect on HD fibroblasts was seen. This teaching of May and Gray is in direct contrast to the teaching of "drug candidate" selection as defined in Claim 1, part d. In Claim 1, part d see the phrase "...but which **does** prevent stress protein expression [emphasis added] in the patient cell culture as per step c(3)." Hence, the teaching of the Examiner's cited prior art is fundamentally different from the teaching of the instant disclosure.

In a fourth flawed interpretation of the cited prior art by the Examiner, the following distinction between May and Gray (1985) and the instant disclosure is presently noted. In the six experimental conditions stated in Claim 1, part c, there is no condition that includes fibroblasts from a patient having a predetermined neurological disease and an agent being investigated and a "stress protein-inducing parameter" [the Applicant's wording, Specification page 19, line 14 and Claim 1, parts c(5) and c(6)]. Yet the analogous conditions of May and Gray (1985), namely Figure 5, are cited by the authors as being their most salient data, their most essential teaching. Hence, this emphasis of May and Gray **teaches away from** the instant disclosure. This is another fundamental difference between the Examiner's cited prior art and the instant disclosure which the Examiner has failed to recognize. It gets to the essential aspect of the instant drug screening invention, since as noted in Claim 1, part d, "a drug candidate of possible clinical value" is defined as an "agent which does not prevent chemically induced stress protein expression in the control cell culture as per step c(6) but which does prevent stress protein expression in the patient cell culture as per step c(3)."

As regards Kawagoe *et al.* (1993), the Applicant wishes to note several distinctions between this prior art and the instant disclosure. To begin with, this prior art relates to a non-human animal model of global ischemia, while the instant disclosure does not relate to either non-human animals or to global ischemia. Furthermore, Kawagoe *et al.* (1993) did not describe studies in fibroblasts of any kind. The word "fibroblast" does not appear in their publication. They used slices of gerbil brain tissue. Their study focused on CA1 cells, which are nerve cells. Also, they did not study proteins. They studied messenger RNA. Studies of this kind on humans are not within the realm of possibility, since obtaining brain samples from living subjects is not feasible. However, in contrast, obtaining *in vitro* cultured fibroblasts from skin biopsy samples is both possible and convenient. This is part of the novelty of the instant disclosure.

In citing Kawagoe *et al.* (1993) in paragraph two of Examiner's Point (12), the Examiner is attempting to claim that "...since cells die upon sufficient levels of stress protein..." induction of HSP70 causes cell death. Hence, the Examiner claims that "...thus by measuring viability May fairly used an indicator system that is capable of detecting stress protein expression." Yet it is well known to those of ordinary skill in the art that "sufficient levels of stress protein" do not cause cell death. Stress proteins help cells *avoid* cell death.

Points (13) and (14) of the Examiner's letter

For reasons set forth in Applicant's letter postmarked 20 August 2005, in the Remarks section entitled "Point (2) of the Examiner's letter" of the present communication and in the Remarks section entitled "Points (11) and (12) of the Examiner's letter" of the present communication, the Applicant has already specifically addressed the distinctions between May and Gray (1985) and the instant disclosure. These previously characterized distinctions make it clear that no credible basis exists for citing May and Gray (1985) as the primary basis of a 35 U.S.C. §103 rejection of Claims 1, 2 and 4.

This being the case, the Examiner's further combination of Berberian WO 91/15219 with May and Gray (1985) still fails to demonstrate that Claims 1, 2 and 4 of the instant disclosure were anticipated by the prior art. For similar reasons, the Examiner's further combination of Ide *et al.* 1995 with May and Gray (1985) and Berberian WO 91/15219 still fails to demonstrate that Claims 1, 2 and 4 of the instant disclosure were anticipated by the prior art. The Examiner's assertion that the instant disclosure was presented earlier in May and Gray (1985) is incorrect for the reasons the Applicant has already enumerated, and the Examiner's attempt to supplement his initial mistake with one of many reports on stress proteins and one of many reports on the huntingtin protein fails to correct the original mistake.

As regards Berberian WO 91/15219, the Applicant also wishes to note the following. The Examiner cannot advocate both sides of an argument. On page 3 of the 21 July 2005 Office letter in Point (2) the Examiner stated that "The indicator system was the percentage of cells which are viable; **since cells die upon sufficient levels of stress protein** [emphasis added] the viability assay corresponds to claim 1(d) as viability tests fairly anticipate use of an indicator system." In paragraph two of examiner's Point (12) of the 27 October 2005 Office letter, the Examiner stated that "...**since cells die upon sufficient levels of stress protein**..." induction of HSP70 causes cell death, according to the Examiner's view of Kawagoe. *et al.* (1993). These assertions by the Examiner were the basis for the Examiner's unjustified claim that the presence of stress proteins and cell death amount to the same thing, and hence in the opinion of the Examiner the trypan blue cell death assay is also an assay for stress proteins. For reasons enumerated above, this assertion of the Examiner has no basis in fact.

Then in Point (14) of the 27 October 2005 Office letter the Examiner cited Berberian WO 91/15219. The title of this prior art is "Method of treatment with HSP70." The abstract begins with the statement that "A method of combating mortality in a cell or tissue under stress is disclosed. The method comprises contacting hsp70 to the cell or tissue in an amount effective to enhance the survival of that cell or tissue." So, in the Examiner's communications he has argued both that heat shock proteins, also known as stress proteins, *cause* cell death and that they can be used as a method of treatment to *avoid* cell death. The applicant presently requests that the Examiner clarify which

side of this contradiction is his real opinion, as it is unreasonable to expect the Applicant to respond to both.

Points (13) and (15) of the Examiner's letter

For reasons set forth in Applicant's letter postmarked 20 August 2005, in the Remarks section entitled "Point (2) of the Examiner's letter" of the present communication and in the Remarks section entitled "Points (11) and (12) of the Examiner's letter" of the present communication, the Applicant has already specifically addressed the distinctions between May and Gray (1985) and the instant disclosure. These previously characterized distinctions make it clear that no credible basis exists for citing May and Gray (1985) as the primary basis of a 35 U.S.C. §103 rejection of Claims 1, 2 and 3.

This being the case, the Examiner's further combination of Berberian WO 91/15219 with May and Gray (1985) still fails to demonstrate that Claims 1, 2 and 3 of the instant disclosure were anticipated by the prior art. For similar reasons, the Examiner's further combination of Ide *et al.* 1995 with May and Gray (1985) and Berberian WO 91/15219 still fails to demonstrate that Claims 1, 2 and 3 of the instant disclosure were anticipated by the prior art. For similar reasons, the Examiner's further combination of Savage *et al.* 1992 with May and Gray (1985), Berberian WO 91/15219 and Ide *et al.* 1995 still fails to demonstrate that Claims 1, 2 and 3 of the instant disclosure were anticipated by the prior art. The Examiner's assertion that the instant disclosure was presented earlier in May and Gray (1985) is incorrect for the reasons the applicant has already enumerated, and the Examiner's attempt to supplement his initial mistake with one of many reports on stress proteins, one of many reports on the huntingtin protein and one of many reports on avidin/biotin antibody detection systems fails to correct the original mistake.

Points (13) and (16) of the Examiner's letter

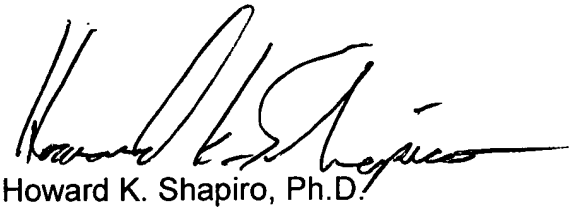
For reasons set forth in Applicant's letter postmarked 20 August 2005, in the Remarks section entitled "Point (2) of the Examiner's letter" of the present communication and in the Remarks section entitled "Points (11) and (12) of the Examiner's letter" of the present communication, the Applicant has already specifically addressed the distinctions between May and Gray (1985) and the instant disclosure. These previously characterized distinctions make it clear that no credible basis exists for citing May and Gray (1985) as the primary basis of a 35 U.S.C. §103 rejection of Claims 1 and 5-8.

This being the case, the Examiner's further combination of Bowling and Beal (1995) with May and Gray (1985) still fails to demonstrate that Claims 1 5-8 of the instant disclosure were anticipated by the prior art. For similar reasons, the Examiner's further combination of Levine *et al.* 1994 with May and Gray (1985) and Bowling and Beal (1995) still fails to demonstrate that Claims 1 and 5-8 of the instant disclosure were anticipated by the prior art. The Examiner's assertion that the instant disclosure was presented earlier in May and Gray (1985) is incorrect for the reasons the Applicant has already enumerated, and the Examiner's attempt to supplement his initial mistake with one of many reports on oxidative stress in neurodegenerative diseases and one of many reports on carbonyl assays for oxidized proteins fails to correct the original mistake.

In closing, the Applicant wishes to note a citation on the Examiner's Form PTO-892 that the Applicant cannot find described in the Examiner's Office action comments. The Applicant refers to citation V on Form PTO-892 page two. This is listed as "Piacentini 1992." The Examiner included a photocopy of this abstract with the copies of his other cited prior art. Actually, the first author is P. Piersanti, and S. Piacentini is the fourth author. This reference was described in the instant disclosure, but at present the Applicant does not understand why it was listed on the Form PTO-892.

In view of the foregoing Amendments and remarks, it is believed that all of the grounds of rejection have been overcome and that the Claims are now fully in condition for allowance. Accordingly, it is requested that the rejections be withdrawn and that a Notice of Allowance be forwarded to the Applicant.

Favorable action is earnestly solicited.



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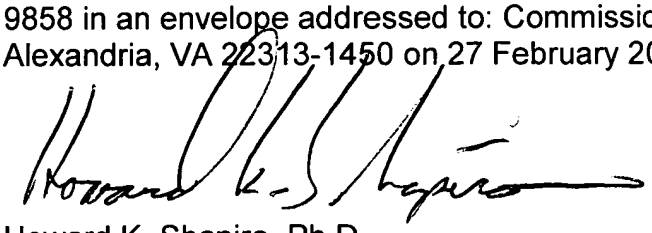

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